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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,658	12/05/2003	Istvan Szelenyi	034082-001	8943

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,658	SZELENYI ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

ETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific sodium channel opener (i.e., flupirtine) in combination with the specific sodium channel (i.e., tolperisone, eperisone, silperisone, etc...), does not reasonably provide enablement for "potassium channel openers in combination with sodium channel-inhibiting or –influencing substance". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claims are directed to use of potassium channel openers in combination with sodium channel-inhibiting or -influencing substances, or of their therapeutically utilizable salts.

Potassium channel openers comprise a structurally diverse group of drug with their pharmacological activity vastly different from each other depending upon their different subtypes and site of action (i.e., pancreas, heart, skeletal muscle, neurons, etc...). For example, potassium channels are classified broadly into two main superfamilies: the inward rectifier (KIR) superfamily (including receptor-coupled, ATP-sensitive and voltage-dependent channels) and the Shker-related superfamily (which includes Ca2+-dependent channels).

Similarly, sodium channel modulators comprise a structurally diverse group of drug with their pharmacological activity vastly different from each other depending upon their different site of action (i.e., brain (Typle I, Type II, Type III), heart (h1) and skeletal muscle (u1)).

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is high. The specification does not provide any competent evidence or disclosed tests that all of "potassium channel openers" or "sodium channel-inhibiting or -influencing substances" that may not necessarily have similar structures would behave similarly as the demonstrated potassium channel opener such as flupirtine and sodium channel inhibitor such as tolperisone. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of

unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

As discussed above, the instant claims embrace numerous types of potassium channel openers (i.e., ATP-activated, voltage-gated (including voltage-dependent and voltage-independent), Ca2+-activated, inward recifiers, etc...) and many distinct types of sodium channel modulators. With respect to the instantly claimed "sodium channel-inhibiting or -influencing substance", the scope of the invention encompasses not only inhibitor, but also partial agonist/antagonist and dual ion channel inhibitor (i.e., dual Na+/Ca2+ channel inhibitor), and etc...

The specification discloses flupirtine as the suitable potassium channel opener and toplperisone and its analogs epersione and silperisone, riluzole, propafenone, lidocaine, flecainide and metixean as the suitable sodium channel-inhibiting or -influencing substances. In addition, the specification shows the effects of flupirtine which activates voltage-independent potassium channel inhibitor in combination with tolperisone which inhibits voltage-dependent sodium channels in increasing muscle tone in rats (Examples).

Although the specification provide enabling disclosure for increasing muscle tone with the administration of flupirtine with toperisone (broadly including its analogs eperisone and silperisone), none of the specification provides enabling disclosure for the entire scope of "potassium channel openers" or "sodium channel-inhibiting or -influencing substances". The instant claims read on all "potassium channel openers", and/or "sodium channel-inhibiting or -influencing substances", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. The skilled artisan would have not expected that any of "potassium channel openers" or

"sodium channel-inhibiting or -influencing substances" that may not necessarily have similar structure behave similarly to the tested flupirtine and toperisone, without undue amount of experimentation.

In view of the nature of the invention, the amount of guidance present in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

2. Claim 1 is rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention claims that the combination of sodium channel-inhibiting or -influencing active compounds and potassium channel openers can be used for treating pains in connection with diseases of an increased muscle tone including neuralgias, arthritis and arthrosis, chronic or episodic tension headache, lower spastic pararesis syndrome, tetraparesis, Parkinsons' disease, and etc...

The specification discloses the evidences which have been incorporated references (Pratzel et al., Pain 1996; 67;417-25 and Bose, Methods Find Exp Clin Pharmacol 1999; 21:209-13) showing the efficacy of sodium channel blocker such as toplperisone or its analogue eperisone in treating painful muscle spasm, which meets the written description. However, claims 1 and 5-11 are directed to encompass any "sodium channel-inhibiting or -influencing substances" and/or "pains which are accompanied by an increase in muscle tone", necessitating an exhaustive search for the embodiments

suitable to practice the claimed invention. None of these meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of tolpersione or its analogs eperisone or silperisone, the skilled artisan cannot envision which "sodium channel-inhibiting or -influencing substances" would be capable of provide the desired effect of the claimed invention, without undue amount of experimentation. Furthermore, with the exception of pain associated with muscle spasm, the skilled artisan cannot envision which types of pain would be responded to the claimed therapeutic agent in combination, without undue amount of experimentation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12 provide for the use of retigabine or its pharmaceutically acceptable salt, in combination with sodium channel-inhibiting or –influencing substance or its pharmaceutical acceptable salt, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Regarding claim 9, the phrase "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 8 recites the broad recitation "pains associated with lower spastic paraparesis syndrome", and the claim also recites "lower paraspasm, transverse myelitis, multiple sclerosis, heritable inferior spastic paraplegia (Stuempel paraplegia), disturbances of the spinal blood circulation and cerebral paralysis involving lower spastic paresis" which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 101

4. Claims 1-12 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-12 are rejected under the judicially created doctrine of double patenting over claims 1-11 of copending Application No. 10/727655, and further in view of Kornhuber et al., J Neural Transm 1999; 106:857-67.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the selection of the specific potassium channel openers such as retigabine and flupirtine would have been apparent to those skilled in the art.

Both of the instant application and the patent are directed to use of potassium channel openers in combination with sodium channel-inhibiting or -influencing

substance, wherein the instant application requires flupirtine as the specific potassium channel opener, whereas the copending application requires the use of retigabine. One having ordinary skilled in the art would have been motivated to select other known potassium channel inhibitor (structurally similar compounds) with the expectation that such substitution would not significantly alter the analogous properties of the compound of the reference due to art-recognized functional equivalent characteristics.

Conclusion

6. No Claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614